## REMARKS

Claims 1-13 were elected without traverse on 6/20/2008, at which time claims 14-22 were withdrawn. With this amendment, claims 14 to 22 are now cancelled.

Claim 1 has been amended to recite the restrictions of claims 4 and 7. Claim 3, 4 and 7 have now been cancelled. Claims 5 and 6 (previously dependent on claim 4) and 8 and 9 (previously dependent on claim 7) have been amended to depend from claim 1.

Claims 1, 2, 5, 6 and 8-13 are currently pending in the instant application.

**1. Rejection of Claims 1, 2, 3 and 7-13 under U.S.C. 102(b) as being anticipated by Kusunoki et al.**

Reconsideration is requested of the rejection of claims 1, 2, 3 and 7-13 under U.S.C. 102(b) as being anticipated by Kusunoki et al. (US 6,143,555).

As amended, claim 1 recites the restrictions of claim 4 which was not deemed to have been anticipated by Kusunoki et al. Thus, the objection is traversed.

**2. Rejection of Claims 1-13 under 35 U.S.C. 103(a) over Kusunoki et al., taken with Mikkelsen et al. and Matsunaga**

Reconsideration is requested of the rejection of claims 1-13 under 35 U.S.C. 103(a) as being unpatentable over Kusunoki et al. (US 6,143,555) hereinafter referred to as the '555 Patent, taken with Mikkelsen et al. (US 6,391,577) hereinafter referred to as the '577 Patent, and Matsunaga (US 4,528,270) hereinafter referred to as the '270 Patent.

As amended, claim 1 of the instant application is directed to:

A method of identifying a microorganism comprising the steps of:

a) obtaining a test sample of an unknown microorganism;

b) adding a mediator or mediator mixture to the test sample in the presence of an effector, wherein the mediator or mediator mixture comprises ferricyanide, dichlorophenol-indophenol (DCIP), ferrocene and ferrocene derivatives, methylene blue, janus green, tris(bipyridyl)iron(III), a quinone, a phenazine, or combinations thereof;

c) assessing variation in respiration rate of the microorganism using electrochemical measurements over a pre-determined time period; and

d) comparing the variation in the respiration rate of the microorganism with the variation in respiration rates of known microorganisms exposed to the effector, thereby identifying the unknown microorganism in the test sample.

**Kusunoki et al.**

Kusunoki et al. (the '555 Patent) teaches a microorganism species inspection apparatus which assesses respiration of cells in test samples under different culture conditions through measurement of changes in dissolved oxygen levels. Microorganisms are identified based on their growth or non-growth in different culture media (e.g. supplemented with drugs) compared to known microorganisms.

The '555 Patent fails to teach measurement of the variation in respiration rate and, more specifically, the utility of such a measurement in the identification of unknown microorganisms, as disclosed in the instant application (page 4, lines 4-12). Changes in basal respiration is measured in the device contemplated in the '555 Patent, but it is used only as a correlate of cell number (see col 3, lines 64-67 and col 5, lines 39-42 of the '555 Patent). The method of identification disclosed by the '555 Patent also requires *a priori* knowledge of the type of microorganism that might be present in the test sample:

> "… a species of micro-organism existing in the liquid… is identified accurately… by preparing the medium to correspond to a species of micro-organism considered to possibly exist in the liquid objected for measurement." (col 3, lines 25-30 of the '555 Patent)
>
> "Therefore, by previously preparing a medium in correspondence to a species of micro-organism possibly existing in the liquid provided for measurement, the species of micro-organism existing in the liquid provided for measurement is identified…" (col 3, lines 59-63 of the '555 Patent)

Thus, it is clear from the above that some prior knowledge is required in order for appropriate test conditions to be pre-selected in the '555 Patent invention. Further, these pre-selected conditions are limited to culture media which either permit growth (survivable) or do not permit growth (non-survivable). These are disclosed as follows:

> "…survivable culture cells and non-survivable culture cells are determined in correspondence to species of micro-organism in the test liquid." (col 5, lines 15-18 of the '555 Patent)

Here again, selection of culture conditions is reliant upon pre-existing inkling of what the "unknown" microorganism may be. The contemplated test conditions do not include intermediates that might produce a characteristic variation in respiration rate of 10 to 600% as disclosed in the instant application (page 7, lines 1-3 of the instant application). Survivable and non-survivable conditions are disclosed in the '555 Patent as follows:

> "Since in the survivable culture cells in which the micro-organism can survive, the dissolved oxygen is consumed by the respiration of micro-organism, electric signals corresponding to the decrease of the dissolved oxygen are output from corresponding oxygen electrodes. On the contrary, since the dissolved oxygen is not consumed in the non-survivable culture cells, electric signals corresponding to the condition that the dissolved oxygen is not decreased, (*sic*) are output from corresponding oxygen electrodes." (col 5, lines 18-26 of the '555 Patent)

The applicants also argue that the apparatus taught by the '555 Patent is limited to direct measurement of dissolved oxygen with oxygen electrodes (recited in claim 1 of the '555 Patent). As such, it can only be applied to aerobic microorganisms. The instant application clearly states that measurement of reduced intermediates is distinct from measurement of dissolved oxygen (page 6, line 4-7 of the instant application) and that the disclosed method may be applied to the identification of aerobic and anaerobic microorganisms (page 6, lines 20-30 of the instant application). Facultative anaerobes are later disclosed (page 8, lines 22-25).

While the Office alleges that the '555 Patent is lacking only in disclosure regarding use of specific mediators, the applicants respectfully argue that the invention is also clearly distinguished by teaching:

1. A method of identifying microorganisms based on measurement of the variation of respiration rate in different culture conditions,

2. A method of identifying microorganisms that does not require *a priori* knowledge of what may or may not be present in the test sample, and

3. A method that is not reliant on dissolved oxygen measurements, and is equally applicable to aerobic and anaerobic organisms.

**Mikkelsen et al.**

The Office alleges that Mikkelsen et al. (the '577 Patent) discloses the use of the specific mediators described the instant application. However, the '577 Patent is clearly directed towards a method for screening drug sensitivity and does not contemplate identification of unknown microorganisms. It fails to teach that specific patterns of variation in drug sensitivities (as determined by measurements of respiration) could be unique to a given species and form a basis for identification. Therefore, while the '577 Patent discloses the specific mediators, there would be no impetus to combine this method with the apparatus of Kusunoki et al. since both references fail to teach the species-specific nature of variations in respiration rates under different growth conditions.

**Matsunaga et al.**

The Office states that Matsunaga (the '270 Patent) teaches that measurement of pick [peak] current potentials relating to cellular metabolic activities can be species-specific and useful for identifying unknown microorganisms. However, the '270 only discloses this measurement for a single condition per species, and does not contemplate variation in respiration rate for a single species. Therefore, it fails to establish that variations in respiration rate under different culture conditions could be useful for identifying an unknown species.

In addition, the '270 Patent clearly teaches that peak current potentials do not correlate with oxidative phosphorylation. The '270 Patent demonstrates that specific inhibition of components of the electron transport chain does not impact peak current and that

> "These results suggest that peak current generation is not correlated with oxidative phosphorylation which occurs inside the mitochondria." (col 5, lines 46-49 of the '270 Patent)

In contrast, specific inhibition of pyruvate dehydrogenase is shown to significantly impact the peak current measurements in the '270 Patent, leading to the following conclusion:

> "… the generation of peak current potential is correlated with pyruvate dehydrogenase and the citric acid cycle." (col 5, lines 53-55 of the '270 Patent)

As outlined above, the method disclosed by the '270 Patent teaches that measurements of citric acid cycle activity may be useful for identification purposes, but teaches away from measurements relating to oxidative phosphorylation. Conversely, the '577 Patent et al. teaches that "The mediator interacts with the terminal components of the respiratory pathway," (col 5, 63-64 of the '577 Patent) i.e. components the electron transport chain which carry out oxidative phosphorylation. Therefore, there would be no impetus for one skilled in the art to combine the mediators taught by the '577 Patent (directed to measurement of oxidative phosphorylation) with the method of measuring of peak current potentials (disclosed as unrelated to oxidative phosphorylation) as taught by the '270 Patent.

With respect to combination of the '555 Patent and the '270 Patent, the former is clearly directed to direct measurement of dissolved oxygen (col 2, lines 49-50 of the '555 Patent) while the method of the latter requires direct contact between living cells and an electrode (claim 1 of the '270 Patent). Indeed, the '270 Patent teaches that covering the electrode with a dialysis membrane which excludes living cells (not solutes) abolished the peak current (col 7, lines 9-12 of the '270 Patent). Therefore, there would be no reason for one skilled in the art to contemplate combination of the method of the '270 Patent with the apparatus for measuring a dissolved gas as taught by the '555 Patent.

**Conclusions**

In summary, claim 1 of the instant application discloses a method for identifying microorganisms based on measuring unique variations in respiration rate under culture conditions that include an effector and with no requirement for *a priori* knowledge about the unknown organism. The applicants submit that the method of claim 1 is inventive and patentable over the cited references for the reasons set forth above with regard to the '555, '577, and '270 Patents. Combination of these references has also been traversed, as technical details would teach away from a blending of the disclosed methods. Claims 2, 5, 6

and 8-13 ultimately depend from claim 1 and are thus patentable over the cited references for the same reasons.

The Application is believed to be in condition for allowance, and favorable action is courteously solicited.

A three-month extension of time is requested under separate cover.

**The Commissioner is hereby authorized to charge any additional fees, and credit any over payments to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.**

Respectfully submitted

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